REMARKS

Claims 27-39 and 41 are pending and under examination in the subject application. No claim has been canceled, amended or added. Accordingly, claims 27-39 and 41 are still pending and under examination in the subject application.

In view of the remarks below, applicants maintain that the Examiner's rejections have been overcome, and respectfully request that they be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 27-39, and 41 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention. Specifically, the Examiner concedes that the specification is enabled for a method of treating a malignant tumor which comprises the administration of the P4C10 β_1 integrin antibody, a β_1 integrin receptor antibody fragment, or a peptide consisting of GRGDSP, but further alleges that it does not reasonably provide enablement for a method of treating a malignant tumor which comprises the administration of any anti-β_1 integrin antibodies.

In response to the Examiner's rejection, applicants respectfully traverse.

The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and the information known in the art without undue experimentation. Applicants maintain that the claimed invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

The subject invention is a method of treating a malignant tumor in a subject which comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein (a) the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and (b) the agent is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2), in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells. Applicants maintain that one skilled in the art could practice the claimed method without undue experimentation.

In support of the rejection, the Examiner alleges that not all antibodies that recognize β_1 integrin will be effective in treating a malignant tumor in light of the unpredictability in the pertinent art.

Applicants disagree with the Examiner's position. Applicants assert that one of skill in the art would not be forced into undue experimentation to practice the instant invention.

In support of this assertion, applicants direct the Examiner's attention to the subject specification *inter alia* at page 41, line 4 to page 42, line 7, which discloses the effect of antibodies directed to β_1 integrin on the inhibitory effects of tenascin on the migration of leukocytes. In these experiments, applicants demonstrated that the inhibition of β_1 integrin with an anti-β_1 integrin antibody stops the inhibitory effects of tenascin. Several anti-β_1 integrin antibodies were used, e.g. P4C10 and $A_{II}B_{II}$, as well as anti-β_2 integrin antibodies to demonstrate the specificity to β_1 integrin. As stated on page 45, lines 28-30, "the interaction of β_1 integrins on PMN and monocytes with cognate ligands on tenascin signals these cells to stop migrating." Applicants maintain that one skilled in the art would recognize from this application that inhibiting binding of β_1 integrin to *tenascin* allows the migration of the leukocytes to their target tumor cells, rather than inhibiting binding of β_1 integrin receptor with any of its ligands. Thus, any antibody that blocks the binding of β_1 integrin to tenascin would be reasonably expected to block the inhibitory effects of tenascin on leukocyte migration. Accordingly, applicants maintain that the claims should be understood in this manner.

In view of the above remarks, applicants maintain that claims 27-39 and 41 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 27, 28, 29, and 41 under 35 U.S.C. §102(b) as allegedly anticipated by Bourdon et al. (WO 92/07872). Specifically, the Examiner stated that "Bourdon et al. disclose a method of inhibiting the attachment of cells to tenascin comprising the administration of a peptide comprising the sequence of SEQ ID NO:2 and further contemplates the use of the method in a human."

In response to the Examiner's rejection, applicants respectfully traverse.

Bourdon et al. teach polypeptides capable of modulating attachment to cells which express the tenascin receptor. Boudon et al. further speculate on the use of such polypeptides in humans to inhibit the attachment of cells to the subcellular matrix thereby preventing the formation of a tumor.

In support of this rejection, the Examiner points to page 32, lines 17-24, of Bourdon et al. which states that "a subject polypeptide, preferably a peptide corresponding to formula p1 or p2, can be used in a pharmaceutically acceptable composition that, when administered to a human subject in an effective amount, is capable of competitively inhibiting cell attachment to the subcellular matrix. That inhibition is believed to result in a decreased rate of tumor formation."

Applicants respectfully disagree with the Examiner's interpretation of the teachings of Bourdon et al. as they

apply to the claimed invention. Under 35 U.S.C. §102(b), a person shall be entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country", more than one year prior to the date of filing the application for patent. According to M.P.E.P. §2131, "[t]o anticipate a claim, the reference must teach every element of the claim."

Claims 27-39 and 40 provide methods of treating a malignant tumor in a subject which comprise administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin. Further, the claimed methods provide that the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and that the agent used in these methods is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2).

Bourdon et al. do not teach treating malignant tumors by inhibiting the effects of tenascin on the migration of leukocytes, which effects enable these leukocytes to reach and kill the tumor cells. Instead, this reference suggests that the inhibition of cell attachment, through competitively binding the tenascin receptor to prevent it from binding to tenascin, may result in a decreased rate of tumor formation. The subject invention does not teach a method for preventing tumor formation, but rather provides a method for treating a

tumor by permitting leukocytes to enter and kill already existing tumor cells.

Further, Bourdon et al. do not teach that leukocytes express the tenascin receptor, that the tenascin receptor is a β_1 integrin cell surface receptor or that the administration of an agent to inhibit the binding of tenascin and the β_1 integrin cell surface receptor must be in an amount effective to inhibit the signaling pathway triggered by such binding thereby enhancing the migration of leukocytes to their intended target tumor cells. Therefore, Bourdon et al. do not teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 27, 28, 29 and 41 satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §102(e)

The Examiner rejected claims 27, 28, 29, and 41 under 35 U.S.C. §102(e) as allegedly anticipated by Ruoslahti et al. (U.S. Patent No. 5,981,478). Specifically, the Examiner stated that "Ruoslahti et al. disclose a method comprising the administration of a peptide sequence that comprises that of SEQ ID NO:2 and wherein the administration is to a human. Furthermore, Ruoslahti et al. disclose that integrins are involved in cancer cell metastasis."

In response to the Examiner's rejection, applicants

respectfully traverse.

Ruoslahti et al. disclose that their "invention provides methods useful for inhibiting metastasis of tumors *expressing integrins* involving administering to an individual a peptide of this invention *that binds to those integrins*." (Column 10, lines 31-34, emphasis added)

Again, applicants respectfully disagree with the Examiner's interpretation of the teachings of Ruoslahti et al. 35 U.S.C. §102(e) states, in relevant part, that a person shall be entitled to a patent unless the invention was described in "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." According to M.P.E.P. §2131, "[t]o anticipate a claim, the reference must teach every element of the claim."

As stated above, the rejected claims provide methods of treating a malignant tumor in a subject which comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin. Further, the claimed methods provide that the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and that the agent used in these methods is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2).

Ruoslahti et al. do not teach treating malignant tumors by inhibiting the effects of tenascin on the migration of leukocytes, but rather teach that the binding of a tumor's integrin receptor inhibits metastasis of these integrin-expressing tumors. Ruoslahti et al. do not teach that the binding of integrin receptor to an RGD peptide prevents binding to tenascin. In fact, Ruoslahti et al. do not teach tenascin or its implication for the treatment of malignant tumors. Further, Ruoslahti et al. do not teach that the administration of an agent to inhibit the binding of tenascin and the β_1 integrin cell surface receptor must be in an amount effective to inhibit the signaling pathway triggered by such binding, but teach instead that the administration of RDG peptides must be in an effective amount to allow for the binding of these peptides to the tumor cells. Therefore, Ruoslahti et al. do not teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 27, 28, 29 and 41 satisfy the requirements of 35 U.S.C. §102(e) and respectfully request that the Examiner withdraw this rejection.

Conclusion

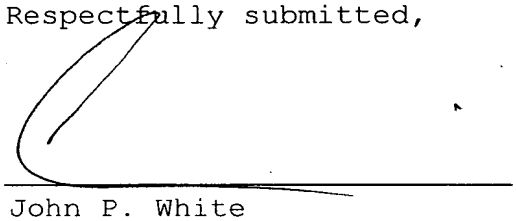
In view of the remarks hereinabove, applicants maintain that the Examiner's rejections have been overcome and that the pending claims are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing

prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any such fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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